UNITED STATES DEPARTMENT OF CO
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEM
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/943,240	09/10/92	LUBIN	30023/105

EXAMINER: CROUCH, D

18M2/0722

FOLEY & LARDNER
SUITE 500
3000 K ST N.W.
WASHINGTON, D.C. 20007-5109

ART UNIT	PAPER NUMBER
1804	8

DATE MAILED: 07/22/93

This is a communication from the examiner in charge of your application
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-15 are pending in the application.
   Of the above, claims _____ are withdrawn from considaretion.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-15 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

PTOL-326 (Rev. 9-89)

EXAMINER'S ACTION

This is a continuation in part of ser. no. 638995, filed January 11, 1991. The preliminary amendment filed January 25, 1993 has been entered.

Claims 1-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 07/638995. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and '995 are drawn to a transgenic non-human mammal, a method of producing protein C and a method of producing a transgenic animal. In the instant specification, claims 1-15 are drawn to a non-human transgenic mammal which produces protein C or an other protein of interest in its milk, when said mammal is comprised of a transgene encoding the genomic sequence for protein C or an other protein of interest, a method of producing protein C and method of producing transgenic animals comprised of genomic sequence for human protein C. In '995, the claims are drawn to a transgenic non-human mammal which expresses a DNA sequence having protein C activity, where the protein C is secreted into the milk of said mammal, a method of producing protein C and a method of making transgenic non-human animals. The claims of the instant application are obvious over the claims of '995 as the genomic sequence for protein C is a DNA sequence having protein C activity. In addition, the DNA sequence of interest in claim 15 of the instant application is obvious over the protein C DNA sequence of claims 1-35 of '995.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

Claims 1-15 provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application Serial No. 07/638995. Briefly, the claims of the instant application and '995 are drawn to a transgenic non-human mammal expressing DNA sequences encoding protein C such that protein C can be identified in the milk of said mammal, a method to produce protein C and a method to produce transgenic animals.

Copending application Serial No. 07/638995 has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. This provisional rejection under 35 U.S.C. § 103 is based upon a presumption of future patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 C.F.R. § 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by another", or by a showing of a date of invention prior to the effective U.S. filing date of the copending application under 37 C.F.R. § 1.131.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 11 is rejected under 35 U.S.C. § 101 because it is drawn to non-statutory subject matter. Claim 11 is drawn to a method of producing transgenic animals, which includes humans. Claims to a method to produce transgenic humans is non-statutory.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description. Claims 1-15 are drawn to a non-human transgenic mammal which secretes protein C into its milk, where the expression of the genomic protein C DNA sequences is regulated by the Sau3A-Kpn1 fragment of the mouse whey acidic promoter operatively linked to a genomic fragment of human protein C where said fragment begins 21 basepairs 5' to the initiation codon of protein C to the NheI site 3' to the termination codon, a process for producing said transgenic mammals and a process of producing

protein C by isolation from the milk of the transgenic mammal. Therefore, DNA sequences which encode the mouse whey acidic promoter, protein C and protein C non-coding regions appear to be critical elements for the instant invention. The specification must identify a readily available and reproducible source for critical elements. Applicant has identified an individual as the source for the cDNA for human protein C. However an individual is a not a readily available or a reproducible source. In addition, applicant has not indicated a reproducible and publicly available source for the genomic DNA fragment encoding human protein C. In order to satisfy the enablement of claims 1-10 and 12, applicant can deposit plasmids WAPpC1 and WAPpC2 for the DNA sequence for protein C, and deposit the Sau3A-Kpn1 fragment of the mouse whey acidic promoter operatively linked to a genomic fragment of human protein C where said fragment begins 21 basepairs 5' to the initiation codon of protein C to the NheI site 3' to the termination codon. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific DNA constructs have been deposited under the Budapest Treaty and that the constructs will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. See 37 CFR 1.808. If the deposit is not made under the Budapest Treaty, then

applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and,

(e) the deposit will be replaced if it should ever become inviable, contaminated or lose the ability to function as disclosed in the specification.

As required under 37 CFR 1.809(d), the specification shall contain: (1) the accession number for the deposit; (2) the date of deposit; (3) a description of the deposited biological material sufficient to identify it and to permit its examination; and (4) the name and address of the depository.

Moreover, applicant is limited to transgenic mice where the transgene is human protein C DNA sequences contained in the Eco RI fragment of WAPpC1 and WAPpC2 regulated by the mouse whey acidic acid protein promoter, or where the transgene is the Sau3A-Kpn1 fragment of the mouse whey acidic promoter operatively linked to a genomic fragment of human protein C where said fragment begins 21 basepairs 5' to the initiation codon of protein C to the NheI site 3' to the termination codon, a process

for producing said transgenic mice and a process of producing protein C by isolation from the milk of said transgenic mice. Applicant has not enable the production of all transgenic mammals which produce heterologous protein C in their milk. The production of transgenic mammals which exhibit tissue specific production of a specific protein is unpredictable. Applicant has not taught nor provided evidence that protein C DNA sequences will integrate into the genome of all mammals and that such integration will permit the production of heterologous protein C in the milk of all mammals. For a transgenic mammal to be enabled, applicant must teach that transgenic embryos resulted in the development of transgenic mammals. In the case of pig, applicant demonstrated that the microinjection technique produced pig embryos containing the transgene integrated into the genome. However the production of such embryos does not indicate that the embryo will develop into a transgenic pig. For example the protein C DNA sequences may have integrated at a site which will prevent the expression of a DNA sequence critical for the development of the pig embryo into a later stage fetus. Since the site of integration can not be controlled the production of transgenic mice which express the protein C transgene, does not mean that the production of transgenic pigs or other transgenic non-human mammals producing protein C will result. For example the mouse whey acid protein promoter may not be recognized by regulatory proteins in sheep mammary gland cells. Regulatory

proteins in a particular animal may not recognize the promoter sequences and expression of the transgene would not occur. Furthermore other mammary gland cell specific promoters may not be recognized by regulatory proteins when used to produce protein C in transgenic mice. The adaptation of mammary gland promoters for the expression of high levels of a protein in the mammary gland of a transgenic mammal is unpredictable. Henninghausen states that the mouse whey acid promoter can produce proteins some 20% above the endogenous WAP gene, the ß-casein gene promoter has not been observed to express a transgene at high levels (Henninghausen (1990) Protein Expression and Purification 1, 3-8, page 4, col. 2, parag. 1, lines 11-21). Thus the limitation of applicant to the whey acid protein gene promoter is valid. In addition, RNases may degrade the RNA expression product or proteases may degraded the protein expression product of the protein C DNA sequences. Applicant has not enabled the production of protein C with modified activity nor has applicant provided guidelines for determining a DNA sequence which encodes protein C activity. The modified protein C on pages 18-19 of the specification discusses possible alterations which can lead to a modification, but are not sufficiently specific to teach production of modified protein C in the mammary gland of non-human transgenic mammals. Applicant has not taught an assay method to determine DNA sequences which encode a protein having protein C activity. Applicant has not taught either DNA sequences

which encode polypeptides with protein C activity or polypeptides with protein C activity. Thus, the skilled artisan is not provided with a reasonable expectation of success and without an undue amount of experimentation in the implementation of the invention of claims 1-15.

Claims 1-15 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1,3,6,11,12 and 14 contain the term "comprises substantially" or "substantially comprising" which is vague and indefinite as the reader can not be sure of other components of the promoter sequence. "Substantially" has no clear definition is the art and is open to broad interpretations. "Comprises" is open ended claim language. Thus the term "comprises substantially" or variations thereof, read as though the promoter sequence contains critical but unclaimed characteristics. In this regard the term is vague and indefinite by not defining the metes and bounds of the claims. Claim 3 is vague and indefinite as the term "variant thereof" is not defined in the claim or specification. It can not be discerned if applicant means a structural or activity variant or some other type of variant. Claim 15 is confusing as it depends on claim 16,

but there is no claim 16.

Claims 1-10 and 12-15 are rejected under 35 U.S.C. § 103 as being unpatentable over Pittius et. al. (1988) Proced. Natl. Acad. Sci. 85, 5874-5878 in view of Grinnell et. al. (1987) Bio/Technology 5, 1189-1192, Brinster et al (1988) Proced. Natl. Acad. Sci. 85, 836-840, Campbell et al (1984) Nucl. Acids Res. 12, 8686-8697 and Clark et al (1987) TIBTECH 5, 20-24. Pittius teaches that tPA can be detected in the milk of a transgenic mouse, when expression of the tPA transgene is regulated by the mouse whey acidic protein promoter and the tPA transgene contains a signal peptide which directs secretion of the protein product into the milk (page 5875, col. 3, parag. 1, line 1 to page 5876, col. 2, through parag. 2 and page 5876, fig. 2). Grinnell teaches the expression of human protein C in tissue culture cells transfected with an expression vector comprised of the cDNA for human protein C and regulatory sequences, where active protein C was isolated from the culture media (page 1191, col. 2, parag. 1). Brinster teaches that the inclusion of intron sequences enhances the expression of a transgene in transgenic mice (see abstract and page 837, fig. 1). Campbell teaches the genomic sequence for mouse protein C (see pages 8691-8692, fig. 3). Clark teaches the production of compounds of pharmaceutical importance in transgenic mammals by the specific expression of DNA sequences which encode a compound of interest in the mammary gland of the transgenic mammal, the secretion of the compound into the milk of

the mammal and the subsequent isolation of the compound from the milk (page 22, col. 1, parag. 2 to col. 2, line 13). Thus given the teachings of the prior art, the ordinary artisan would be provided a reasonable expectation of success in producing protein C or any other protein of interest in the milk of a transgenic non-human mammal expressing protein C or a protein of interest, where the transgene is comprised of the genomic sequence for protein C or a protein of interest operatively linked to the mouse whey acidic promoter. The 4.2kb Sau3A-Kpn1 fragment of the whey acidic promoter is obvious over the smaller fragment taught by Pittius, as the optimization of expression would be within the scope of skills of the ordinary artisan. In addition the specific genomic protein C DNA sequence would be a matter of choice on the part of the inventor.

Claim 11 is rejected under 35 U.S.C. § 103 as being unpatentable over Colpan et.al. (1984) Journal of Chromatography 296, 339-353 in view of Hogan et. al. (1986) Manipulation of the Mouse Embryo, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY. pages 153-203. Colpan teaches the purification of plasmid DNA by anion exchange HPLC. Hogan states that DNA for the production of transgenic animals must free of contaminants which may harm the egg. New uses for known methods do not necessarily overcome the art in the absence of unexpected results. In the absence of side by side comparisons, the purification of DNA for the production of transgenic non-human mammals by HLPC is the

functional equivalent of other methods for purification such as CsCl gradient centrifugation. Thus the ordinary artisan with the teachings of the prior art would have been offered a reasonable expectation of success in the production of the transgenic non-human mammal as claimed when the DNA construct comprising the transgene had been purified by HPLC.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Deborah Crouch

Deborah Crouch
Patent Examiner
Art Unit 1804

Dr. D. Crouch
July 21, 1993